

*Current Concepts***VENOUS THROMBOEMBOLISM
DURING PREGNANCY**

MARC R. TOGLIA, M.D., AND JOHN G. WEG, M.D.

VENOUS thromboembolism is an uncommon but leading cause of illness and death during pregnancy and the puerperium.^{1,2} It has been reported to occur in 1 in 1000 to 1 in 2000 pregnancies,^{3,4} although few studies have used objective diagnostic techniques. Over the past two decades, there has been considerable change in the management of venous thromboembolism in non-pregnant patients. Moreover, our understanding of changes in the coagulation system during pregnancy has increased. However, the management of venous thromboembolism during pregnancy remains a subject of controversy because of the lack of prospective clinical trials. In this article, we will summarize our current knowledge and present a rational approach to management.

PATHOPHYSIOLOGY

The risk of venous thromboembolism is five times higher in a pregnant woman than in a nonpregnant woman of similar age.⁵ The increased venous stasis of pregnancy is the most constant predisposing factor. Physiologic changes associated with pregnancy result in an increase in venous distensibility and capacity; these changes are evident from the first trimester.^{6,7} The venous system of the lower extremities is particularly vulnerable to thrombosis as a result of compression by the gravid uterus. Several independent obstetrical factors have also been shown to be associated with an increased risk of thromboembolic disease, including prolonged bed rest during pregnancy or the puerperium, instrument-assisted or cesarean delivery, hemorrhage, sepsis, multiparity, and advanced maternal age.⁸

Pregnancy is also associated with marked alterations in the proteins of the coagulation and fibrinolytic systems. The levels of coagulation factors II, VII,

and X increase substantially by the middle of pregnancy.^{9,10} The generation of fibrin also increases markedly.¹¹⁻¹³ Levels of protein S appear to decrease throughout pregnancy, although levels of protein C remain normal.^{12,14} The fibrinolytic system is also inhibited, most substantially in the third trimester.^{12,15,16}

Recently, resistance to activated protein C, due to a point mutation in the gene coding for factor V, has been reported as a predisposing factor for venous thromboembolism. In one study involving almost 15,000 subjects, the presence of such resistance was associated with a three-to-sevenfold increase in the risk of venous thromboembolism; this may be the most common hereditary cause of hypercoagulation.¹⁷ A few recent studies have implicated resistance to activated protein C as a cause of thromboembolism during pregnancy, although its exact role in the process is still unknown.¹⁸

Traditionally, the risk of thrombosis has been considered greatest during the third trimester and immediately post partum. During an era when it was common for physicians to discourage mothers from walking for a week or more post partum, it was reported that two thirds of all thromboembolisms associated with pregnancy occurred after delivery.¹⁹ Other obstetrical practices once common, such as the use of oral estrogen to suppress lactation and operative vaginal delivery, may also have contributed to this pattern.²⁰ More recent investigations, however, all of which required objective criteria for diagnosis, have suggested that the majority of the thromboembolisms associated with pregnancy occur ante partum. In the largest study to date, Rutherford et al.⁴ reported that 75 percent of deep-vein thromboses occurred ante partum, with 51 percent of the thromboses taking place by the 15th week of gestation. In contrast, 66 percent of pulmonary emboli occurred post partum. Other researchers have reported that venous thromboembolism occurs with almost equal frequency in all three trimesters.²¹⁻²³

DIAGNOSIS**Deep-Vein Thrombosis**

During pregnancy, thrombosis most frequently begins in the veins of the calf or in the iliofemoral segment of the deep venous system and has a striking predilection for the left leg.^{21,23,24} Our ability to diagnose deep-vein thrombosis clinically is generally poor and is further hampered during pregnancy since swelling of the patients' legs and the attendant discomfort occur commonly. Noninvasive studies, such as impedance plethysmography (IPG), real-time B-mode ultrasonography, and duplex Doppler ultrasonography, have replaced venography for most nonpregnant patients.²⁵ A single noninvasive study showing evidence of thrombosis is considered sufficient to justify treatment; therapy may be safely

From the Department of Obstetrics, Gynecology, and Reproductive Medicine, State University of New York at Stony Brook (M.R.T.); and the Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor (J.G.W.). Address reprint requests to Dr. Togliola at the Department of Obstetrics, Gynecology, and Reproductive Medicine, Health Sciences Center T9, Room 033, State University of New York at Stony Brook, Stony Brook, NY 11794-8091.

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withheld if serial studies are negative.^{26,27} Preliminary research on the use of these techniques in pregnant women has been promising.^{7,24,28} Beginning in the late second trimester, these procedures should be performed with the uterus displaced laterally, because compression of the iliac veins and vena cava by the gravid uterus can produce false positive results.^{7,28,29} These noninvasive studies are less sensitive in detecting calf-vein thrombosis than more proximal thromboses. Magnetic resonance imaging may also be of value in detecting thromboses in the femoral, iliac, and ovarian veins during pregnancy.³⁰

Venography is widely held to be the standard for establishing a diagnosis of deep-vein thrombosis.²⁵ Some authorities still recommend that positive results of noninvasive studies should be confirmed by venography before a pregnant woman is exposed to the risks of prolonged anticoagulation; the risks to the fetus caused by the radiation used in venography are negligible (Table 1).³¹ Venography should be performed if noninvasive studies are equivocal or if serial noninvasive studies cannot be performed.

We recommend that either IPG or ultrasonography be the initial diagnostic tool in pregnancy. Patients with a clinical presentation suggestive of deep-vein thrombosis and positive results on a noninvasive study should receive anticoagulant therapy. Patients who, on clinical evidence, are likely to have thrombosis but whose initial test results are negative should undergo either venography or serial noninvasive testing. The results of one study support the withholding of anticoagulant therapy in pregnant women with clinical indications of deep-vein thrombosis but negative results on serial IPG.²⁴

Pulmonary Embolism

Signs and symptoms indicative of pulmonary embolism must be interpreted with caution during pregnancy, because dyspnea, tachypnea, and discomfort in the legs are common, particularly at term. Electrocardiograms, chest radiographs, and arterial-blood gas measurements may support the diagnosis or suggest other conditions. During the third trimester, arterial oxygen tension may be as much as 15 mm Hg lower in the supine position than in the sitting position,³² so values for arterial-blood gases should be obtained with the patient in the upright position during the last trimester.

The ventilation-perfusion scan is the primary screening tool for the diagnosis of pulmonary embolism in both pregnant and nonpregnant patients. The findings of the Prospective Investigation of Pulmonary Embolism Diagnosis study support the use of ventilation-perfusion scanning as a sufficient basis for clinical decisions when the results are interpreted as normal or as indicating a high probability of embolism. Otherwise, pulmonary angiography is nec-

TABLE 1. ESTIMATED RADIATION ABSORBED BY THE FETUS IN PROCEDURES TO DIAGNOSE VENOUS THROMBOEMBOLIC DISEASE.*

PROCEDURE	ESTIMATED RADIATION
	μGy
Unilateral venography without abdominal shield	3140
Limited venography	<500
Pulmonary angiography by femoral route	2210–3740
Pulmonary angiography by brachial route	<500
Perfusion lung scanning with technetium-99m macroaggregated albumin (1–2 mCi)	60–120
Ventilation lung scanning	
With technetium-99m sulfur colloid	10–50
With technetium-99m pentetate	70–350
With xenon-133	40–190
Chest radiography	<10

*Modified from Ginsberg et al.,³¹ with the permission of the publisher.

essary to rule out pulmonary embolism.³³ Physicians are often reluctant to perform radiologic studies during pregnancy because of concern about the effects of radiation on fetal development. However, the estimated exposure of the fetus to radiation during these examinations is small. The combination of chest roentgenography, ventilation-perfusion scanning, and pulmonary angiography exposes the fetus to less than 5000 μGy (0.5 rad) (Table 1).³¹ Exposure to radiation of less than 50,000 μGy (5 rad) has not been associated with a significant risk of fetal injury in most studies.³¹

Some clinicians advocate performing either IPG or sonography of the legs before angiography in nonpregnant patients in whom a ventilation-perfusion scan shows a low or intermediate probability of embolism. Patients with positive noninvasive studies should be treated for pulmonary emboli. Patients with negative studies should undergo angiography, because noninvasive studies may be negative in up to 57 percent of nonpregnant patients with angiographically demonstrated pulmonary embolism and ventilation-perfusion scans showing a low or intermediate probability.³⁴ The efficacy of such an approach in pregnant patients is unclear. Moreover, noninvasive studies are likely to miss emboli that originate in the pelvic veins during pregnancy.

A diagnosis of venous thromboembolism has major implications for pregnant patients, given the need for prolonged therapy with heparin during pregnancy, the potential need for prophylaxis during subsequent pregnancies, and concern about patients' future use of oral contraceptive pills and estrogen-replacement therapy. Because of these issues and the gravity of the diagnosis, we recommend strongly that the possibility of venous thromboembolism be

aggressively investigated with definitive studies whenever it is suspected in a pregnant patient.

MANAGEMENT

Extensive clinical experience and retrospective cohort studies have established heparin to be the safest anticoagulant to use during pregnancy, because it does not cross the placenta.³⁵ Initially, intravenous heparin therapy should be given according to the current recommendations for nonpregnant patients (Table 2).³⁶⁻³⁸ The duration of therapy will depend on when the thromboembolism occurred in the pregnancy.

Warfarin should be avoided throughout pregnancy. Its use during the first trimester has been associated with a characteristic embryopathy.^{39,40} Pathologic effects on the fetus, such as central nervous system and ophthalmologic abnormalities, have been associated with exposure to warfarin in any trimester.^{39,40} Warfarin readily crosses the placenta and can result in fetal and neonatal hemorrhage and placental abruption.³⁹ Some authorities recommend the use of warfarin during pregnancy for specific patients, such as women with mechanical heart valves, those who have a recurrence while receiving heparin, and those with contraindications to heparin therapy. If warfarin is used during pregnancy, patients must be fully informed about the potential adverse effects on the fetus.

Antepartum Venous Thromboembolism

Women with venous thromboembolism during pregnancy should receive intravenous heparin for 5 to 10 days. Subcutaneous heparin should then be

continued with an adjusted-dose regimen for the remainder of the pregnancy (Table 3). This recommendation is supported by the results of a prospective, randomized trial in nonpregnant patients, which reported a recurrence rate of 47 percent with a dose of 5000 IU given subcutaneously every 12 hours.⁴¹ Anticoagulant therapy should be continued post partum with heparin and warfarin; heparin can be discontinued once the level of anticoagulation with warfarin is adequate. Warfarin should be continued for six weeks post partum, or until at least three months of anticoagulant therapy have been completed.^{35,42}

A regimen of adjusted-dose, subcutaneous heparin for nonpregnant patients has been well described.³⁸ Concentrated heparin (20,000 IU per milliliter) should be administered every 12 hours to maintain either a mid-interval activated partial-thromboplastin time 1.5 times the control value or a plasma heparin level of 0.1 to 0.2 IU per milliliter. Alternative methods of administering heparin include a subcutaneous pump^{43,44} and the use of low-molecular-weight heparin. The use of low-molecular-weight heparin during pregnancy is particularly attractive because it needs to be given only once daily and its use may reduce the risk of heparin-induced thrombocytopenia⁴⁵ and heparin-induced osteoporosis.⁴⁶ Experimental evidence suggests that low-molecular-weight heparin does not cross the placenta.⁴⁷ Data on the use of low-molecular-weight heparins during pregnancy are encouraging, but clinical experience with these agents is still limited.^{48,49}

Filters in the inferior vena cava have been used safely and effectively in pregnant women.^{50,51} Supra-

TABLE 2. PROTOCOL FOR ADJUSTMENT OF THE DOSE OF INTRAVENOUS HEPARIN.*

ACTIVATED PARTIAL-THROMBOPLASTIN TIME (SEC)†	REPEAT BOLUS?	STOP INFUSION?	NEW RATE OF INFUSION	REPEAT MEASUREMENT OF ACTIVATED PARTIAL-THROMBOPLASTIN TIME
<50	Yes (5000 IU)	No	+3 ml/hr (+2880 IU/24 hr)	6 hr
50-59	No	No	+3 ml/hr (+2880 IU/24 hr)	6 hr
60-85‡	No	No	Unchanged	Next morning
86-95	No	No	-2 ml/hr (-1920 IU/24 hr)	Next morning
96-120	No	Yes (for 30 min)	-2 ml/hr (-1920 IU/24 hr)	6 hr
>120	No	Yes (for 60 min)	-4 ml/hr (-3840 IU/24 hr)	6 hr

*A starting dose of 5000 IU is given as an intravenous bolus, followed by 31,000 IU per 24 hours, given as a continuous infusion in a concentration of 40 IU per milliliter. The activated partial-thromboplastin time is first measured six hours after the bolus injection, adjustments are made according to the protocol, and the activated partial-thromboplastin time is measured again as indicated. Adapted from Hirsh.³⁶ For an alternative protocol, see Cruickshank et al.³⁷ and Hull et al.³⁸

†The normal range, measured with the Dade-Actin-FS reagent, is 27 to 35 seconds.

‡The therapeutic range of 60 to 85 seconds is equivalent to a heparin level of 0.2 to 0.4 IU per milliliter by protamine titration or 0.35 to 0.7 IU per milliliter according to the level of inhibition of factor Xa. The therapeutic range varies with the responsiveness of the reagent used to measure the activated partial-thromboplastin time to heparin.

TABLE 3. RECOMMENDATIONS FOR THE TREATMENT OF THROMBOEMBOLIC DISEASE DURING PREGNANCY.

CONDITION	RECOMMENDATION
Antepartum deep venous thrombosis or pulmonary embolism	Intravenous heparin for 5 to 10 days,* followed by adjusted-dose subcutaneous heparin given every 12 hours to prolong the activated partial-thromboplastin time measured 6 hours after the injection to a value 1½ times the control value until delivery.† Warfarin administered post partum for at least 6 weeks or to complete 3 months of anticoagulation.
Postpartum deep venous thrombosis or pulmonary embolism	Intravenous heparin for 5 to 10 days,* followed by warfarin for at least 3 months.

*Dosage to be adjusted according to the recommendations in Table 2.

†Or to maintain plasma heparin levels at 0.1 to 0.2 IU per milliliter.

renal placement is recommended. No important maternal or fetal morbidity associated with the filters has been reported. The indications for their use are the same as in nonpregnant patients: any contraindication to anticoagulant therapy; serious complication of anticoagulation, such as heparin-induced thrombocytopenia; and the recurrence of pulmonary embolism in patients with adequate anticoagulant therapy. The use of thrombolytic agents during pregnancy has been limited to life-threatening situations because of the risk of substantial maternal bleeding, especially at the time of delivery and immediately post partum.⁵² The risk of placental abruption and fetal death due to these drugs is currently unknown.

Labor and Delivery

Anticoagulant therapy rarely presents a problem at delivery, but it is still unclear whether therapy with heparin should be altered or discontinued during labor. It is reasonable to instruct patients to discontinue heparin at the onset of regular uterine contractions, although some investigators have recommended that a dose of 5000 IU of subcutaneous heparin be given every 12 hours throughout labor.⁵³ The risk of maternal hemorrhage during vaginal delivery is minimal, especially when plasma heparin levels are less than 0.4 IU per milliliter.^{23,53} The decision to use regional anesthesia must be made on an individual basis, with the small but definite risk of spinal hematoma weighed against the benefits of regional anesthesia. Some authorities believe that regional anesthesia is not contraindicated if the activated partial-thromboplastin time is normal and heparin has not been administered within four to six hours before the procedure.⁵⁴ Blood loss at the time of cesarean section is not markedly increased.⁵⁵ Protamine sulfate can be administered to patients with markedly prolonged activated partial-thromboplastin times or supratherapeutic plasma heparin levels at the time of delivery.⁴²

Postpartum Venous Thromboembolism

The treatment of a patient in whom a venous thromboembolism develops post partum is similar to that of a nonpregnant patient. Warfarin should be given for at least three months to minimize the risk of recurrence.⁴² Neither heparin nor warfarin therapy is a contraindication to breast-feeding.³⁵ Because warfarin is teratogenic, reliable contraception is essential.

COMPLICATIONS OF TREATMENT

Some early retrospective studies suggested that heparin was associated with an increased incidence of miscarriage and prematurity.³⁹ However, more recent analyses^{35,56} support the drug's safety and efficacy. Osteopenia induced by heparin has been reported in pregnancy,^{57,58} although it is usually associated with the administration of at least 20,000 IU per day for more than six months.³⁵ The osteopenia appears to be reversible in most cases.⁵⁸ Whether women who receive long-term therapy with heparin during pregnancy are predisposed to fractures in the future is unknown. In one retrospective study,⁵⁹ women who had undergone long-term therapy with heparin were more likely than untreated women to have a bone density of less than 1.0 g per square centimeter, although none had fractures.

PROPHYLAXIS

Among women with a history of thromboembolism during pregnancy, the incidence of recurrence during a subsequent pregnancy has been estimated to be 4 to 15 percent.^{60,61} Recent data suggest that these women may have an increased risk of recurrent thrombosis because, as compared with controls, they have higher plasma levels of biochemical markers of activation of the coagulation cascade during subsequent pregnancies.⁶²

Because of the paucity of prospective studies, firm clinical guidelines for antepartum prophylaxis are difficult to establish. A recent consensus conference recommended that pregnant women with a history

of venous thromboembolism receive 5000 IU of subcutaneous heparin every 12 hours.³⁵ However, higher doses of heparin may be required for effective prophylaxis during pregnancy to offset the characteristic increases in plasma volume, renal clearance, and blood levels of coagulation factors and to counteract the alterations in the metabolism of heparin.^{53,62} A few authorities, however, advocate giving no prophylaxis.⁶⁰

In a recent prospective study of prophylaxis with heparin during pregnancy, sufficient subcutaneous heparin in adjusted doses was administered to maintain a plasma concentration of 0.08 to 0.15 IU per milliliter (average dose, 16,400 IU per day).⁵³ The amount of heparin required increased throughout the second and third trimesters, but decreased slightly at term. There were no recurrences of thromboembolism. The same investigators later reported that in a series of 184 pregnant women treated with this regimen, there were only five recurrences.⁶³

We believe that pregnant women at risk for venous thromboembolism require more aggressive prophylaxis than has traditionally been recommended. We suggest that such women receive subcutaneous heparin, starting as early as possible in pregnancy, in a dose adjusted to maintain a plasma heparin level of 0.1 to 0.2 IU per milliliter (Table 4). Plasma heparin levels should be monitored every few weeks throughout the pregnancy and more frequently in the last 10 weeks. If heparin levels cannot be readily measured, if the patient's compliance with treatment is a concern, or if the adjustment of dosage is not feasible for other reasons, the subcutaneous administration of 7500 to 10,000 IU of heparin twice daily is an adequate compromise. Preliminary data suggest that this level of therapy with heparin in pregnant women has been associated with an acceptable degree of risk with respect to both bleeding and osteoporotic fractures.^{53,63} Since pregnancy and the puerperium encompass 10 to 11 months, and given the concern about the long-term administration of

heparin in doses greater than 20,000 IU daily,^{57,58} we recommend treatment with warfarin alone post partum.

Women with a known hypercoagulable state or a history of venous thromboembolism unrelated to pregnancy are at increased risk for thromboembolism during pregnancy and should receive prophylactic anticoagulant therapy (Table 4). Patients with a deficiency of antithrombin III have a 70 percent incidence of thrombosis during pregnancy,^{64,65} so anticoagulant therapy is indicated throughout pregnancy.

Patients with a deficiency of protein C or protein S may have a lower risk of thromboembolism during pregnancy than patients with antithrombin III deficiency; venous thromboembolism has been reported in 33 percent of patients with a deficiency of protein C and 17 percent of patients with a deficiency of protein S.⁶⁶⁻⁶⁸ The risk of thrombosis appears to be greatest during the postpartum period in women with protein S deficiency.⁶⁸

Patients with the antiphospholipid-antibody syndrome have an increased risk of both venous and arterial thrombosis, recurrent fetal losses, and other adverse outcomes of pregnancy.⁶⁹ Recently, therapy with warfarin adjusted to maintain an international normalized ratio of at least 3.0 has been recommended as the best regimen for the prevention of recurrent thrombosis in nonpregnant patients with the antiphospholipid-antibody syndrome.⁷⁰ Since warfarin therapy is associated with embryopathy and fetal loss, however, it is recommended that pregnant patients with the antiphospholipid-antibody syndrome who do not have a history of venous thrombosis receive a prophylactic regimen of heparin, and that those with previous thrombosis receive an adjusted-dose regimen of heparin.³⁵ Most authorities recommend that women with prosthetic heart valves also receive an adjusted-dose regimen throughout pregnancy, even though the efficacy of heparin has not been established.³⁵

TABLE 4. RECOMMENDATIONS FOR ANTEPARTUM PROPHYLAXIS.

CONDITION	RECOMMENDATION
Any condition (e.g., antithrombin III deficiency, presence of mechanical prosthetic heart valve, or valvular disease) normally requiring long-term anticoagulant therapy	Adjusted-dose subcutaneous heparin to prolong the activated partial-thromboplastin time to 1½ to 2 times the control value throughout pregnancy.* Warfarin should be started immediately post partum.
Antiphospholipid-antibody syndrome with a history of venous thromboembolism	
History of venous thromboembolism	Either adjusted-dose subcutaneous heparin to maintain a plasma heparin level of 0.1 to 0.2 IU/ml or 7500 to 10,000 IU of subcutaneous heparin twice daily. Warfarin should be given post partum for 6 weeks.
Protein C or protein S deficiency	
Antiphospholipid-antibody syndrome without a history of thromboembolism	

*Or to maintain plasma heparin levels at 0.2 to 0.4 IU per milliliter.

CONCLUSIONS

Pregnancy should be recognized as initiating a hypercoagulable state that encompasses a period of 10 to 11 months. It is likely that the amount of heparin required during pregnancy is greater than previously recognized, yet there is legitimate concern about the prolonged use of heparin in pregnant women. Low-molecular-weight heparins seem promising for use during pregnancy because of their longer half-life and potentially fewer side effects. Controlled clinical trials are desperately needed to ascertain the risk of recurrent thrombosis in pregnancy and to determine the most efficacious use of heparin.

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